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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/038,135	10/20/2001	Bruce N. Ames	B00-001-2	7465

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EXAMINER	
JONES, DWAYNE C	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 09/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/038,135	AMES ET AL.	
	Examiner	Art Unit	
	Dwayne C Jones	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *the amendment and declaration of 11JUN04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 62-131 are pending.

2. Claims 62-131 are rejected.

Response to Arguments

3. Applicants' arguments and declaration filed June 11, 2004 have been fully considered but they are not persuasive. Applicants present the ensuing arguments. First, applicants purport that the instantly claimed primary N-hydroxylamines are functionally and structurally different compounds than the secondary N-hydroxylamines of the prior art reference of Krishna et al.

4. However, its is first noted that the function of the instantly claimed N-hydroxylamine-containing compounds is the same, in particular the cytoprotective effects against reactive oxygen species as well as methods of screening N-hydroxylamine-containing compounds, as that with the N-hydroxylamine-containing compounds of Krishna et al. In addition, one having ordinary skill in the art would have been motivated to use primary N-hydroxylamines to offset the deleterious effects of reactive oxygen species to cells when the prior art specifically teaches that secondary N-hydroxylamines also perform this very same function. For this reason, the skilled artisan would expect that compounds with primary N-hydroxylamines would also reduce the effects of reactive oxygen species to cells because the only structural difference lies with the presence of absence of a hydrogen atom attached to the functional group of the

N-hydroxylamine moiety. Moreover, the skilled artisan would even expect that the structurally-related compounds of primary N-hydroxylamines would react more readily than the secondary N-hydroxylamines due to the absence of a secondary carbon-containing moiety, thus decreasing the steric hinderence of the secondary N-hydroxylamine. The amount and level of skill involved with substituting "bulky" groups, such as alkyl moieties for less "bulky" groups, such as a hydrogen atom, is well within the level of the skilled artisan. In fact, the replacement of an alkyl group for a hydrogen atom is expected and obvious, rather than as purported by applicants as unexpected and nonobvious because of the difference in steric hinderence between a primary N-hydroxylamine and a secondary N-hydroxylamine. Furthermore, one having ordinary skill in the art would have been motivated to use closely-related N-hydroxylamine-containing compounds and their derivatives, which clearly embraces primary N-hydroxyl amines due to the fact that the reaction between the unwanted reactive oxygen species, is with the N-hydroxylamine-containing moiety.

5. Likewise, the declaration of June 11, 2004 presents arguments that are expected to the skilled artisan, namely (1) that the reaction between the reactive oxygen species lies with the oxygen scavenging ability that is inherent with the N-hydroxylamine moiety and (2) functionally and structurally related compounds to those of Krishna et al would obviously and predictably reside with the primary N-hydroxylamine-containing compounds that are instantly claimed. In addition, it is well established through case law "that it is not difficult matter to carry out a process in such a fashion that is would not be successful and, therefore, the failures of experiments who have no interest in

succeeding should not be accorded great weight", see *In re Michalek*, 74 USPQ 108, at 109 citing *Bullard Company et al. v. Coe*, 147 F.2d. 568, 64, USPQ 359. Accordingly, the remarks set forth by Mr. Ames in the declaration that was proffered to obviate the prior art teachings, lacks probative force accorded data and remarks generated by independent, disinterested parties. Thus, the prior art reference of Krishna et al. renders the instant invention obvious.

Information Disclosure Statement

6. The information disclosure statement filed December 8, 2003 fails to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 117 and 120 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *reducing* neuronal cell death induced by beta amyloid peptide or amyloid beta peptide-induced locomotor impairment, does not reasonably provide enablement for being able to "*protect* against amyloid beta peptide-induced neuronal cell death" or "*protect* against amyloid beta peptide-induced locomotor

impairment". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The instant invention is directed to being able to "*protect* against amyloid beta peptide-induced neuronal cell death" or "*protect* against amyloid beta peptide-induced locomotor impairment" with the screened compounds. The method comprises administering N-hydroxylamines.

(2) The state of the prior art

The compounds of the inventions are N-hydroxylamines. However, the prior art does not teach that these compounds of N-hydroxylamines possess these types of properties, see Krishna et al.

(3) The relative skill of those in the art

The relative skill of those in the art of pharmaceuticals is high.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements functioning the same in different circumstances, yielding predictable results, but chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. Supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re Fischer, 427 F.2d 833, 839, 166 USPQ 10, 24 (CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5 (BDAI 1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22

(holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art; In re Wright, 999 F.2d 1557, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the physiological or pharmaceutical activity of N-hydroxylamines and the protection of neuronal cells from beta amyloid-induced cell death or locomotor impairment prior to filing of the instant invention was an unpredictable art.

(5) The breadth of the claims

The instant claims are very broad. For instance, claim 117 is directed to for being able to "*protect* against amyloid beta peptide-induced neuronal cell death". The breadth of claims was a factor in Amgen v. Chugai Pharm. Co., 927 F.2d 1200, 18 USPQ2d (Fed. Cir.),cert. Denied, 502 U.S. 856 (1991). In the Amgen case, the patent claims were directed to DNA sequences that encoded amino acid sequences. Because a very small change in the amino acid sequence of a protein can result in a very large change in the structure-function activity of a protein and because the laws of protein folding are in such a primitive state, predicting protein structure (and hence, activity) while knowing only the sequence of the protein is akin to predicting the weather for a date in the future.

(6) The amount of direction or guidance presented

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fisher, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fischer, 427 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575. In the instant case, given the unpredictability of the physiological or pharmaceutical activity of N-hydroxylamines to be effective in for being able to "*protect* against amyloid beta peptide-induced neuronal cell death" or "*protect* against amyloid beta peptide-induced locomotor impairment" is insufficient for enablement. The specification provides no guidance, in the way of enablement for being able to "*protect* against amyloid beta peptide-induced neuronal cell death" or "*protect* against amyloid beta peptide-induced locomotor impairment other than *reducing* neuronal cell death induced by beta amyloid peptide or amyloid beta peptide-induced locomotor impairment. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Accordingly,

this is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S. 5, by Samuel S. Levin covers this subject in detail. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds that fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

(7) The presence or absence of working examples

As stated above, the specification discloses N-hydroxylamines to be effective in for being able to "*protect* against amyloid beta peptide-induced neuronal cell death" or "*protect* against amyloid beta peptide-induced locomotor impairment". However, the instant specification only has enablement for *reducing* neuronal cell death induced by beta amyloid peptide or amyloid beta peptide-induced locomotor impairment

(8) The quantity of experimentation necessary

The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in determining whether "undue experimentation" is required to make and use the instant invention. "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine how the instant compounds could effectively N-hydroxylamines to be effective in for being able to "*protect* against amyloid beta peptide-induced neuronal cell death" or "*protect* against amyloid beta peptide-induced locomotor impairment" that would be enabled in this specification.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 66, 67, 69-91, 93, 94, 101-106, 113-115 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claims 66, 67, 69-91, 93, 94, 101-106, 113-115 recite the limitation "C1-C18" compounds over ten carbon atoms, such as "N-(n-dodecyl)hydroxylamine", "N-(n-decahexyl)hydroxylamine", "N-(n-decaoctyl)hydroxylamine", "anthryl", "phenanthryl" for

instance in claims 66, 67, 69, respectively. There is insufficient antecedent basis for this limitation in the claim. Moreover, any compound that possesses more than ten carbon atoms, as defined by claim 64, and depends from claim 64 does not have antecedent basis for these compounds.

12. Claims 66, 69, 72, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 111, and 114 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claims 66, 69, 72, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102, 105, 111, and 114 recite the limitation "R" in each of these claims. There is insufficient antecedent basis for this limitation in the claim because there is claim dependency on claim 64.

Claim Rejections - 35 USC § 103

14. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

15. The rejection of claims 62-131 under 35 U.S.C. 103(a) as being unpatentable over Krishna et al. is maintained and repeated for both the above-stated and reasons of record. Krishna et al. teach of the protective effects of inter alia hydroxylamines. Krishna et al. teach that cellular damage may result from the cytotoxicity of reactive oxygen species, (see column 1, page 3477). Krishna et al. also teach that the reactive oxygen species are byproducts of normal processes in aerobic environments, and when there are imbalances in these reactive oxygen species oxidative stress results to cells,

(see page 3477). Krishna et al. also disclose that hydroxylamines have been shown to protect mammalian cells exposed to reactive oxygen species, such as super oxide, hydrogen peroxide, organic hydroperoxides, and redox cycling and anticancer agents, (see column 2, page 3478). In addition, Krishna et al. teach of screening methods to test the effectiveness of hydroxylamines to provide protection to mammalian cells that are exposed to a reactive oxygen species, namely hydrogen peroxide. The results were performed with an in vitro assay, (see column 2, page 3478). In the assay model of this teaching the efficacy of the antioxidant, such as hydroxylamine, was evaluated by exposing the cells to a reactive oxygen species, namely hydrogen peroxide, and assessing the viability of the cells both in the absence and in the presence of a fixed concentration of the test compound, (see column 2, page 3480). The assessment would compare the amounts of the reactive oxygen species present, while the instant invention is comparing the amounts of the antioxidant of the hydroxylamine present after contact with the cells. There are many ways to measure the concentration of an assay, such as a decrease in the concentration of the unwanted species or compound, (as in Krishna et al.) or still by measuring the concentration of the antioxidant compound of the hydroxylamine (as is obviously claimed by applicant).

16. The instant claims differ only in screening methods for primary hydroxylamines whereas the prior art reference of Krishna et al. are directed to screening methods with the utilization of secondary amines. The skilled artisan would most certainly been motivated from the screening methods of Krishna et al. to employ other antioxidant or cytoprotective hydroxylamine compounds to protect cells from the deleterious effects

due to oxidative damage due to inter alia, reactive oxygen species. The generation of reactive oxygen species, as taught by Krishna et al., is evident in many various biochemical and aerobic environments. Accordingly, if a cellular event such as from a variety of scenarios, for instance ischemia or inflammation or cancer or cytokines or still other events, which can generate and cause oxidative damage to a cell, would be obviously protected with the presence of hydroxylamine compounds, as clearly taught by Krishna et al. Clearly, it would have been obvious to the skilled artisan to utilize other hydroxylamine compounds and derivatives, which would obviously include primary hydroxylamine compounds and their derivatives, because the reaction between the oxidative damage lies between the reactive oxygen species and they hydroxylamine moiety. The skilled artisan would additionally be motivated to use primary hydroxylamine compounds and their derivatives especially since the hydroxylamine moiety of a primary hyrdroxyl amine is less sterically hindered than a primary hydroxylamine compound.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (571) 272-0578. The examiner can normally be reached on Mondays, Tuesdays, Thursday, and Fridays from 8:30 am to 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, may be reached at (571) 272-0951. The official fax No. for correspondence is (703) 872-9306.

Also, please note that U.S. patents and U.S. patent application publications are no longer supplied with Office actions. Accordingly, the cited U.S. patents and patent application publications are available for download via the Office's PAIR, see http://pair-direct.uspto.gov. As an alternate source, all U.S. patents and patent application publications are available on the USPTO web site (www.uspto.gov), from the Office of Public Records and from commercial sources.

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DWAYNE JONES
PRIMARY EXAMINER

Tech. Ctr. 1614
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